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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/383,789	08/26/1999	BENJAMIN LEE HUGHES	X-12013	7041

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EXAMINER	
LUKTON, DAVID	
ART UNIT	PAPER NUMBER
1653	22

DATE MAILED: 01/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/383,789	HUGHES ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *123-132, 134-140, 142, 144-153, 155-161, 163, 165-172, 174-180, 182, 184-194* is/are pending in the application.

4a) Of the above claim(s) *127, 144-153, 155-161, 163, 165-172, 174-180 and 182* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *123-126, 128-132, 134-140, 142, 184-194* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Pursuant to the directives of paper No. 21 (filed 10/15/02), claims 123, 134, 142, 144, 155, 163, 165, 168, 174, 180, 182, 184-194 have been amended, claims 122, 133, 141, 143, 154, 162, 164, 173, 181, 183 cancelled, and claims 184-194 added. Claims 123-132, 134-140, 142, 144-153, 155-161, 163, 165-172, 174-180, 182, 184-194 are pending.

Claims 127, 144-153, 155-161, 163, 165-172, 174-180 and 182 are withdrawn from consideration, since none of these claims encompass the elected specie. Claims 123-126, 128-132, 134-140, 142, 184-194 are examined in this Office action.

Applicants' arguments filed 10/15/02 have been considered and found not persuasive with regard to the enablement rejection.

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The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 123-126, 128-132, 134-140, 142, 184-194 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In the declaration filed 2/5/02 (paper No. 18), the results of an experiment are presented. A healthy (non-diabetic) dog was infused with glucose, and subsequently forced to inhale

the peptide Val^8-Glp-1(7-37). The time course of plasma glucose was compared with that of a "sham". The result is that the increase in glucose over the time period of about 30-60 minutes following glucose infusion was less than that observed with the "sham" inhalation. The claims require that one achieve "normalization" of blood glucose in hyperglycemic patients. However, applicants have not provided sufficient evidence that such normalization can be achieved. Applicants have argued that the issue of enablement rests on whether one can demonstrate that a given GLP-1 peptide is effective to reduce serum glucose, and that one need not consider the question of whether the given GLP-1 peptide will raise serum glucose. However, even if it is true that one need not consider the question of whether the given GLP-1 peptide will raise serum glucose, there is more to the analysis than has been presented so far. To begin with, pulmonary adminstration of compounds frequently results in a "pulsatile" delivery, i.e., a rapid rise in serum concentration followed by a rapid fall. Thus, controlling the concentration of the compound that is present in the bloodstream at any given point in time is not necessarily a straightforward matter. To make matters more complicated, there may be a delay in the effect of the compound that has been adminsitered, so that a plot of concentration of the delivered compound as a function of time would not necessarily coincide with a plot of various pharmacological effects of the administered compound. The situation in the instant case is further complicated because of the rise of plasma glucose that occurs merely by subjecting the animal to the pulmonary

adminstration procedure, even without active compound (i.e., the "sham"). Applicants have not offered any explanation for the increase in gluose that occurs in the case of the sham adminstration. Perhaps one explanation is that the adminstration procedure raises the level of epinephrine in the test animal, which causes a rise in glucose. If so, then the serum glucose response to the "sham" inhalation procedure might not be reproducible; for example, a dog which had experienced the "sham" inhalation procedure ten times previously might not be as "unnerved" by the procedure as a dog who had never experienced it previously. The fact that this glucose rise occurs does not necessarily mean that the experimental design is "fatally" flawed, but it is a complicating factor. Adding to the confusion is the absence of any indication as to when the glucose infusion was halted. It is stated in the declaration (paper No. 18, filed 2/5/02) that glucose was administered at a rate of 18 mg/kg/min; there is no indication as to when the glucose infusion was terminated. In addition to this deficiency of information, an important control experiment is lacking, one which would show the plasma glucose level in a dog which was not subjected to a "sham" or to a GLP-1 peptide, but which is simply subjected to whatever glucose infusion that the other three dogs were subjected to. As matters currently stand, the graph (appendix "A", declaration, paper No. 18, filed 2/5/02) does not actually indicate a reduction of glucose concentration that was present an hour after glucose infusion was started. If this control experiment were done, one would expect the glucose concentration of the dog subjected to

pulmonary adminstration of the GLP-1 peptide to fall convincingly below the level of glucose in the dog which was subjected only to glucose infusion. Based on the results presented so far, there is no way to know whether this would be the result obtained.

Another question which has bearing on the issue of enablement of "normalizing" glucose is that of the significant variability of the glucose concentration in diabetic patients. At times, the glucose concentration might be very high, such as after a meal ("postprandial" glucose). At other times, the glucose level might be too low. Thus, there is often a vacillation in the glucose level, as opposed to a situation in which a healthy animal is administered glucose at a steady rate so as to produce a steady state level of glucose. In a situation where the glucose level is vacillating wildly, it would not be a simple matter to tightly control the glucose level using only a compound which is effective to reduce the glucose level. And as indicated above, the quest for the ideal glucose level is made all the more difficult by the "pulsatile" pharmacokinetics resulting from pulmonary administration. Finally, there is no "guidance" in the specification on any of these matters. It appears that the term "normalizing glucose" is only mentioned briefly on page 5, lines 19-21, and only then, it is in regard to unspecified GLP-1 peptides, not necessarily those to which the claims are directed.

In accordance with the following, enablement for the claimed invention is lacking. It is suggested that applicants provide evidence that the claimed peptides are actually effective

to reduce the plasma glucose concentration in hyperglycemic animals; the claim could then be drawn to a method of reducing the plasma glucose concentration.

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Claims 123-126, 128-132, 134-140, 142, 184-194 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- The claims are indefinite as to the process steps and endpoint. One option would be to recite that the peptides are administered *for a time and under conditions effective to mitigate hyperglycemia.* Another option would be to recite that the the peptides are administered *for a time and under conditions effective to lower plasma glucose* (assuming there is descriptive support).

- Claim 184 recites that position 8 of the GLP-1 peptide contains a valine, glycine or methylalanine residue. However, the meaning of "position 8" is ambiguous. Normally, in the absence of any indication to the contrary, one would expect that position "1" is the N-terminal residue, and that position 8 is the amino acid which is seven residues removed from the N-terminal residue. However, in the instant case, applicants have, throughout the specification and remaining claims, designated the N-terminal residue as being position 7, rather than position 1. There is nothing inherently "wrong" with designating the N-terminal residue as being position 7, as long as it is made clear. However, claim 184 does not make this clear. Thus, the N-terminal residue in claim 184 might be designated position 1, it might be designated as position 7, or it could be something else. The claim should be amended to make clear what the counting system is.

*

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 123-126, 128-132, 134-140, 142, 184-194 are rejected under 35 U.S.C. §103 as being unpatentable over Drucker (USP 5846937) in view of Galloway (USP 5705483); or Smith (USP 5908830) in view of Galloway; or Knudsen (WO 98/20895) in view of Galloway; or Danley (EP 0,619,322) in view of Galloway; or Kirk (WO 93/18785) in view of Galloway. As indicated previously, Smith teaches (col 9, line 14 and col 19, line 53) the use of a GLP-1 agonist which can be adminstered (col 11, line 58) by pulmonary means.

Drucker teaches (col 8, line 50; col 9, line 31) administration of one or more GLP analogs by pulmonary means. Knudsen teaches (p. 8, line 25) admininstration of GLP peptides by pulmonary means. Danley teaches (p. 4, line 32) administration of GLP by pulmonary means. Kirk (WO 93/18785) teaches nasal administration of GLP peptides. None of these teach the specific GLP peptide to which the instant claims are drawn. Galloway ('483) teaches (col 5, line 21) that Val^8-GLP-1 resists the proteolytic action of DPP-IV.

Applicants' declaration (paper No. 18, filed 2/5/02) is acknowledged. However, it shows

only that the rise in glucose is less than for the "sham" administration. The results presented do not amount to a showing of "unexpected" results for the reasons given above in the §112, first paragraph rejection. Accordingly, this rejection targets the peptide Val^8-GLP-1(7-37) per se, and it targets other GLP-1 analogs as well.

Thus, the claims are rendered obvious.

*

Claims 123-126 are rejected under 35 U.S.C. §103 as being unpatentable over Galloway (USP 5,705,483).

The teachings of Galloway were indicated previously. Although Galloway discloses intravenous (and other parenteral forms of) administration, Galloway does not disclose administration by inhalation. However, the rejected claims do not actually require such. The rejected claims require only that some of the peptide reach the lungs. It may be the case that, following intravenous adminstration, only 1% of the total peptide adminstered ever reaches the lungs; it might even be 0.1% of the total. However, one of ordinary skill would have expected that, if a radiolabelled drug were adminstered systemically to a rat (or other laboratory animal), at least a small portion of the radiolabel could be detected in lung tissue. Thus, the claims are rendered obvious.

It is noted that claim 182 is dependent on a cancelled claim (claim 173).

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800